REMARKS

Reconsideration of this application is respectfully requested. Claims 12-25, 27, 29 and 31-40 are pending. Claims 12-25, 27, 29 and 31-38 are withdrawn. Claims 39 and 40 are currently at issue.

Rejections under 35 U.S.C. § 103(a) for obviousness

Claims 39 and 40 have been rejected as being obvious over Meijer *et al.* U.S. Patent 6,352,825 (Meijer '825), in view of Stewart *et al.* Journal of Virology, 1996, vol. 70, page 3127 (Stewart *et al.*), Buck *et al.* BioTechniques, 1999, vol. 27, page 528 (Buck *et al.*), Day *et al.* Biochem. J., 1990, vol. 267, page 119 (Day *et al.*) and Lukhtanov *et al.* U.S. Patent 6,339,147 (Lukhtanov '147). This ground for rejection is respectfully traversed.

The probe defined by SEQ ID NO: 12 is not obvious over the cited prior art

The Examiner states that while Stewart *et al.* does not disclose an HPV-59 type-specific oligonucleotide probe identical to SEQ ID NO: 12, Stewart *et al.* does disclose an HPV-59 sequence encompassing the sequence disclosed by SEQ ID NO: 12. The Examiner points out that neither Meijer '825 nor Stewart *et al.* disclose selecting a nucleic acid probe for detection from a known nucleic acid sequence, but that Buck *et al.* does disclose a method for making primers from a known nucleic acid sequence. The Examiner states that one of ordinary skill in the art would have been motivated to use the HPV-59 sequence provided by Stewart *et al.* and the method disclosed by Buck *et al.* to construct a probe as defined by SEQ ID NO: 12.

Buck *et al.* disclose a method of selecting a nucleic acid probe for DNA sequencing, not for the HPV sub-type specific detection of DNA amplified from a clinical sample, as called for by the claims of the present invention. In order to function as an HPV sub-type specific nucleic acid sequence probe, the oligonucleotide sequence defined by SEQ ID NO: 12 must be capable of hybridization to labeled DNA amplified from a clinical sample, wherein detection of the label indicates the presence of HPV DNA in the sample which corresponds to the probe to which the DNA is hybridized (*See* claims 39 and 40). Each of the nucleic acid sequence probes defined by

SEQ ID NOS: 1-19 correspond to a different HPV sub-type (*See* page 9, line 30 through page 10, line 11 of the specification). Therefore, in order for a nucleic acid sequence probe to indicate the sub-type specific presence of HPV-59, it must preferentially hybridize with HPV-59 labeled DNA from the amplified clinical sample, and provide a signal strong enough to be detected over the other eighteen HPV sub-type specific probes that are also present on the DNA chip (*i.e.* SEQ ID NOS: 1-11 and 13-19). There is no teaching or suggestion in Meijer '825, Stewart *et al.* or Buck *et al.* directing one of ordinary skill in the art to select the 30 nucleotide segment of the HPV-59 DNA sequence corresponding to SEQ ID NO: 12 from the 455 nucleotide sequence disclosed by Stewart *et al.* in order to achieve selective hybridization of HPV-59 DNA over the HPV sub-types defined by SEQ ID NOS: 1-11 and 13-19. In addition, Meijer '825 teaches a different HPV-59 sub-type specific probe (*See* SEQ ID No: 49, Table 2, column 20, line 50 in Meijer '825) teaching away from the probe defined by SEQ ID NO: 12.

Furthermore, even if a person of ordinary skill in the art chose to follow the teachings of Buck *et al.* in order to design a nucleic acid probe for the sub-type specific hybridization of HPV-59 DNA, this would amount to nothing more than a starting point for experimentation. First, Buck *et al.* disclose a number of different primer design methods, and fail to teach a single preferred method. Second, a nucleic acid probe for DNA sequencing must necessarily begin at the 5'-end of the DNA being sequenced, thus restricting the region of nucleic acid sequence from which the probe may be designed and limiting the number of possible probe sequences. A nucleic acid probe used for detection, as in the present invention, may be complimentary to any portion of the DNA sequence to be hybridized. The number of possible nucleic acid probes that can be created from a nucleic acid sequence increases with each base-pair contained in the sequence. Therefore, the selection and optimization of any individual nucleic acid probe from the multitude of possible probes would require undue experimentation. Buck *et al.* fails to teach how any single probe would be selected from the plurality of probes that may be created from a nucleic acid sequence of over 450 nucleotides (*See* nucleic acid search report GenBank Accession number U45932, cited in the Office Action).

The methods called for by claims 39 and 40 are *different* and *non-obvious* over the method disclosed by Meijer '825

The Examiner further asserts that one of ordinary skill in the art would have been motivated to use the HPV type-specific oligonucleotide probes on a chip for the diagnosis of HPV because Meijer '825 discloses that the probes are specific for the detection of HPV.

Meijer '825 teaches a method for the diagnosis of HPV infection comprising the steps of (i) amplification of HPV DNA from clinical samples using the primers GP5+ and GP6+; (ii) electrophoresis of the amplified DNA; (iii) transfer of the amplified DNA to a Southern Blot; (iv) hybridization of this Southern Blot with HPV-specific oligonucleotide probes, either singly or as a probe cocktail comprising multiple individual probes; and (v) detection of the hybridized HPV-specific oligonucleotide probes. Thus, in this method the amplified DNA is immobilized and the HPV oligonucleotide probes serve as detection agents when hybridized to the immobilized amplified DNA (see, *e.g.*, column 13, lines 14-19 and column 18, lines 9-45 of Meijer '825).

This *method is different from that of claims 39 and 40 of the present invention*, which comprises the steps of (i) amplifying DNA from clinical samples using primers, such as GP5+ and GP6+ to obtain biotin-containing amplified DNA; (ii) hybridization of this biotin-labeled DNA to a DNA chip comprising a combination of each of the HPV-specific oligonucleotide probes of SEQ ID NOS: 1-19 immobilized on a glass slide; and detecting hybridized DNA on the DNA chip. Thus, in the method of the present invention the HPV-specific oligonucleotide probes are immobilized on a glass slide and the amplified DNA serves as a detection agent when hybridized to the immobilized HPV-specific oligonucleotide probes.

This difference in the two methods is not trivial, for at least the reason that each method results in vastly different hybridization kinetics. In the method of Meijer '825 the immobilized nucleic acid sequence is significantly larger, approximately 5 fold larger, than that of the hybridized nucleic acid. Specifically, the size of DNA amplified by the primers GP5+ and GP6+ is approximately 150 nucleotides (*See* Genbank entry AF548859 for the partial DNA sequence of HPV type 51 showing the position of each primer of the pair, submitted as Exhibit A in the

amendment filed April 7, 2006 in response to the non-final Office Action dated December 7, 2005), while the HPV-specific oligonucleotides are each only 30 nucleotides in length (*See* oligonucleotides a through x as set forth at column 9, line 10 through column 10, line 1 of Meijer '825). Conversely, in the method of the present invention, the immobilized nucleic acid (the HPV-specific oligonucleotides, each of which is 30 nucleotides in length, see SEQ ID NOs:1-19) is significantly smaller that the hybridized nucleic acid (the biotin-labeled amplified DNA, which is approximately 150 nucleotides in length, as discussed for Meijer '825).

One of ordinary skill in the art would readily appreciate that this difference in the size of the immobilized nucleic acid (~150 nucleotides in the method of Meijer versus 30 nucleotides in the method of the invention) would have significant effects on the hybridization kinetics of each method (see, *e.g.*, the abstract of Stillman and Tonkinson. *Anal Biochem* 2001;295:149-157, submitted as Exhibit B in the amendment filed April 7, 2006 in response to the non-final Office Action dated December 7, 2005). For at least this reason (*i.e.*, difference in hybridization kinetics due to size of immobilized nucleic acid), one of ordinary skill in the art would not assume that the method of Meijer '825 would be operative when the amplified DNA was hybridized to an immobilized HPV-specific oligonucleotide, as called for in the present claims.

One of ordinary skill in the art would further appreciate that the difference in the size of the hybridized nucleic acid (~30 nucleotides in the method of Meijer '825 versus ~150 nucleotides in the method of the present invention) would have significant effects on the hybridization kinetics of each method (see, *e.g.*, the abstract of Chan *et al. Bio phys J* 1995;69:2243-2255, submitted as Exhibit C in the amendment filed April 7, 2006 in response to the non-final Office Action dated December 7, 2005). For at least this reason (*i.e.*, difference in hybridization kinetics due to size of hybridized nucleic acid), one of ordinary skill in the art would not assume that the method of Meijer would be operative when the amplified DNA was hybridized to an immobilized HPV-specific oligonucleotide. Furthermore, Chan *et al.* teaches away from the present invention in that it teaches that the hybridized nucleic acid should be about 100 nucleotides or less, whereas in the method of the present invention the hybridized nucleic acid is about 150 nucleotides. Thus, one of ordinary skill in the art would not have been motivated to alter the method of Meijer '825 to provide a

method wherein the amplified DNA was hybridized to an immobilized HPV-specific oligonucleotide, as called for by claims 39 and 40 of the present invention.

Neither Day *et al.* or Lukhtanov '147 remedy the deficiency of Meijer '825 or Stewart *et al.*

The Examiner also states that one of ordinary skill in the art would have been motivated to modify the method of Meijer '825 by using a biotinylated primer for detecting HPV as taught by Day *et al.*, and a Schiff base-type covalent linkage to attach the oligonucleotide to the solid support as taught by Lukhtanov '147, in order to make the DNA chip with SEQ ID NOS: 1-19 for the diagnosis of HPV.

Neither Day *et al.* or Lukhtanov '147 provide a teaching or suggestion that remedies the deficiency of either Meijer '825 or Stewart *et al.* Specifically, neither Day *et al.* nor Lukhtanov '147 teach or suggest hybridization kinetics that would contradict the teachings of Stillman and Tonkinson or of Chan, and thereby provide one of ordinary skill in the art of an expectation of success for the diagnosis of HPV sub-types using a modified version of Meijer '825, wherein the amplified DNA is hybridized to an immobilized HPV-specific oligonucleotide. In addition, neither Day *et al.* or Lukhtanov '147 teach or suggest a method of selecting an HPV-59 sub-type specific nucleic acid sequence as defined by SEQ ID NO: 12 from the HPV-59 nucleic acid sequence disclosed by Stewart *et al.*

In summary, the prior art of record, either alone or in combination, does not render obvious the HPV nucleic acid sequence probe as defined by SEQ ID NO: 12, or the method called for by claims 39 and 40 of the present invention. In view of the foregoing, the Examiner is respectfully requested to withdraw the rejection of claims 39 and 40.

In view of the preceding comments and amendments, it is respectfully submitted that claims 39 and 40 are in condition for allowance and such action is earnestly solicited.

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Respectfully submitted,

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